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(71) *Sökande* / *Applicant (s)* AstraZeneca AB, Södertälje SE

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

NEW PHARMACEUTICAL COMPOSITION

Field of invention

The present invention relates to a new oral pharmaceutical composition comprising NO-donating Non Steroidal Antiinflammatory Drugs.

Futhermore, the invention refers to a method for the manufacture of such pharmaceutical preparations and the use of such preparations in medicine.

Background of the invention

Non-steroidal anti-inflammatory drugs, commonly and hereafter abbreviated as NSAIDs, are well-known drugs for the treatment of pain and inflammation. One of the major drawbacks with NSAIDs is that they have severe gastro-intestinal side-effects. Patients undergoing treatment with NSAIDs for a longer period of time, such as naproxen, often experience problems with stomach gastrointestinal side-effects.

Nitrogen oxide donating NSAID compounds (in the following NO-donating NSAIDs), have recently been found to have an improved side-effect profile, see e.g. WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

NO-donating NSAIDs are lipophilic compounds with poor aqueous solubility. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited, resulting in poor bioavailibility upon oral administration.

Many of the NO-donating NSAIDs are obtained as such, in the form of an oily substance. Therefore, the conventional methods, for instance, tabletting are not applicable on these substances. Oily medicines have generally been produced and put on the market in soft gelatine capsules. The NO-donating NSAIDs in oily form cannot, in its pure form, be compressed into a conventional tablet.

One advantageous solution to the problem to handle oily substances and to obtain dosage form for oral administration is forming a Self Emulsifying Drug Delivery System, commonly known as SEDDS, see WO 01/66087. More particularly, the SEDDS is a pharmaceutical composition suitable for oral administration, in the form of an emulsion pre-concentrate, comprising one or more NO-donating NSAID(s); one or more surfactants; and optionally together with an oil or semi-solid fat. The composition forms *in-situ* oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids. The pre-concentrate emulsion is usually filled into conventional capsules.

Tabletted compositions comprising an oily, sticky active agent and a method for producing these compositions are described in WO 99/27912 and WO 99/ 27913. These documents describe adsorption of the oily sticky component into a porous carrier. However, compositions comprising NO-donating NSAIDs in oily form are not mentioned or proposed in any of these documents and no compressed tablets comprising NO-donating NSAIDs are hitherto known.

One of the unique features with NO-donating NSAIDs is that many of these compounds are oils or thermosoftening semisolids which are practically insoluble in water. With high-dose NO-donating NSAIDs, e.g. when the dose is above about 350 mg, it is difficult to formulate a tablet of reasonable size of the large amount of oil or semisolid.

In the attempts to make conventional tablets comprising NO-donating NSAIDs, such as NO-donating naproxen, a so-called high dose drug, the result has been a too large tablet. The patient compliance can in this case be discussed. The dose administered is preferably 750 mg, i.e. a dose having an affect on the tablet size.

NO-donating NSAIDs are prepared according to the disclosure in WO 94/04484, WO 94/12463, WO 95/09831 and WO95/30641, which are hereby incorporated by reference.

These document do also show that the NO-donating NSAID compounds have an improved side-effect profile.

Outline of the invention

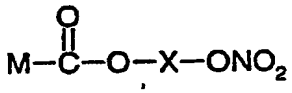
NO-donating NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by Amidon et al. *(Pharm. Res. 12 (1995) pp. 413-420).* Drugs of this class are characterised by low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited, resulting in poor bioavailibility upon oral administration. One object of the invention is to provide an oral formulation with satisfactory bioavailability.

Active substance

The wording "NSAID" is defined as a non-steroidal anti-inflammatory drug, i.e. any drug having an anti-inflammatory effect, but which compound does not belong to the compound class "steroids". A person skilled in the art will recognise a compound that falls under the definition NSAID. Examples of specific NSAIDs are naproxen, diclofenac, aceclofenac, indomethacine, ketorolac, sulindac, meloxicam, piroxicam, tenoxicam, ibuprofen, ketoprofen, naproxen, azapropazon, nabumetone, carprofen, tiaprofenic acid, suprofen, indoprofen, etodolac, fenoprofen, fenbufen, flurbiprofen, bermoprofen, pirazolac, zaltoprofen, nabumetone, bromfenac, ampiroxicam, and lornoxicam. This list should however not be considered as exhaustive in any way. The wording "NO-donating NSAID"

is contemplated to include any non-steroidal anti-inflammatory drug (NSAID), a salt or an enantiomer thereof, which has the capability to release nitrogen oxide.

NO-donating NSAIDs that can be used in the compositions in accordance with the present invention, are compounds of the formula I

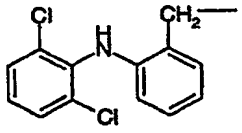


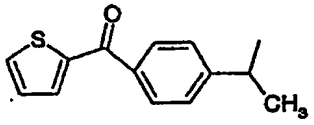
I

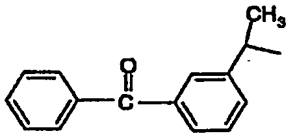
wherein

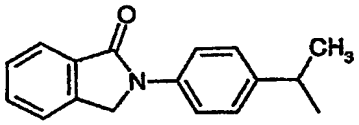
X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID; and

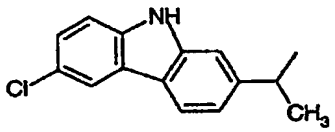
M is selected from anyone of

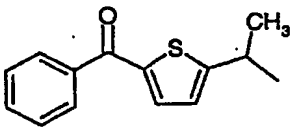


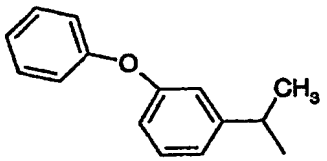


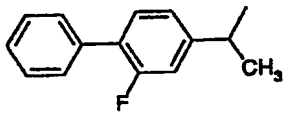


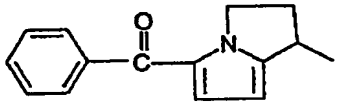


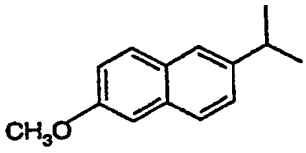


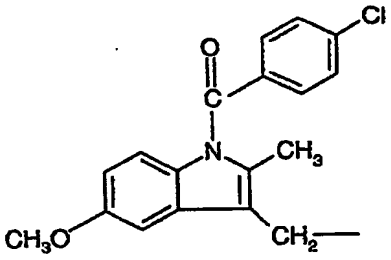


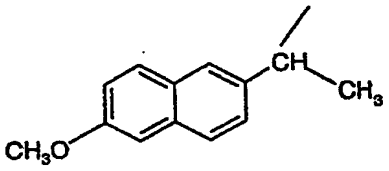


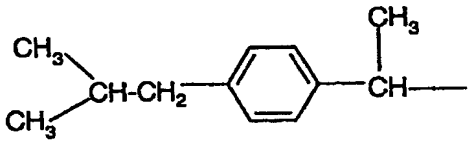












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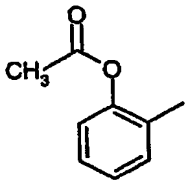
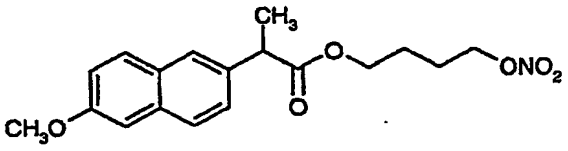


or a salt or an enantiomer thereof. In a preferred embodiment of the invention, the spacer X is selected from a linear, branched or cyclic alkylene group $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; and $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$ wherein p is an integer of from 2 to 10.

In one embodiment of the invention, NO-donating NSAIDs contemplated as active compound(s) in the formulation according to the present invention, are compounds disclosed and claimed in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641, which are hereby incorporated by reference.

Specific NO-donating NSAIDs useful in accordance with the present invention are



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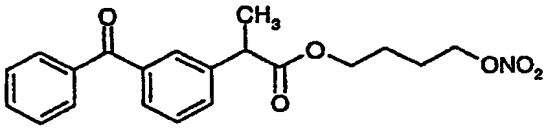

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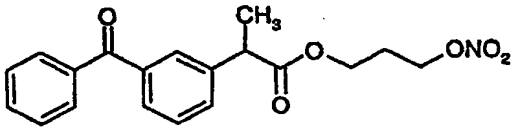

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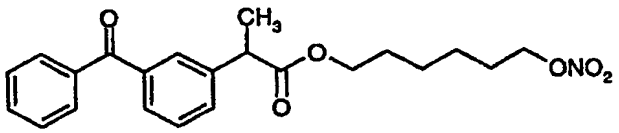

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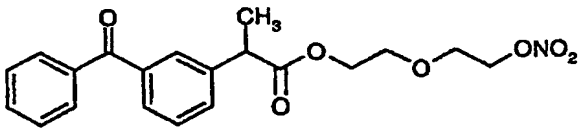

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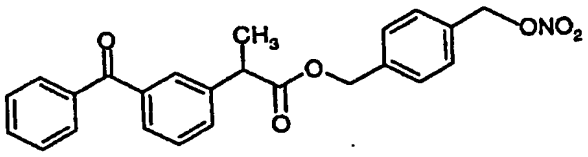

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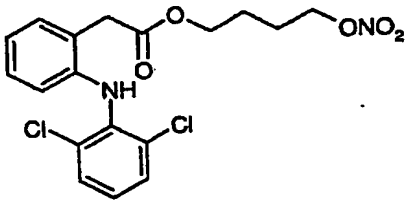

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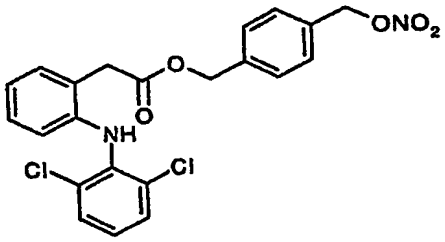

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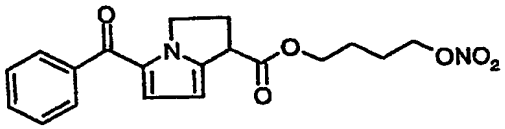

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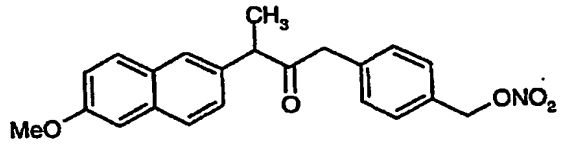

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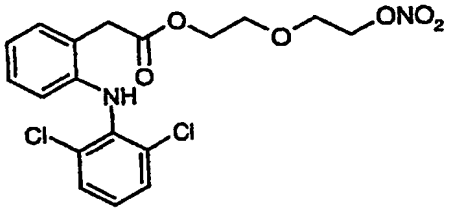

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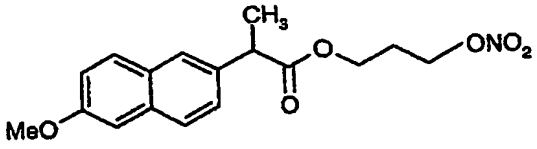

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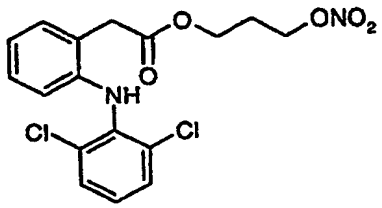

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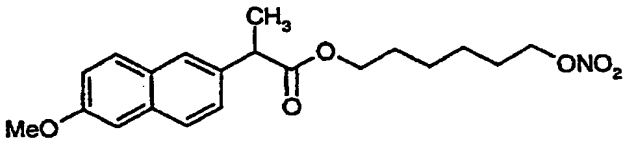

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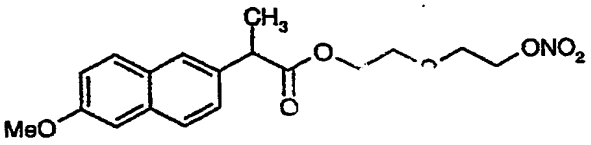

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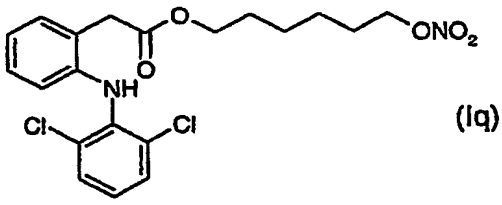


(Iq)

Pharmaceutical formulation

A new way of formulating the NO-donating NSAID in oily form is to adsorb it into porous carriers. Useful carriers for the NO-donating NSAIDs are carriers having properties such

as a high oil-absorbing capacity, so the drug easily adsorbs into the carrier. Also, the carrier must have a good liquid-holding ability, the volume of active ingredient must be kept to guarantee the dose administered.

Further, to control the release from the tablet, a SEDDS-mixture of the NO-donating compound may be adsorbed to the porous particles.

The inorganic porous particles of the porous particle material used for adsorbing the NO-donating NSAID and for carrying the substance in a pharmaceutical dosage form is, for example, calcium silicate, known under the trade name Florite®, dibasic calciumphosphate anhydrous, known under trade name Fujicalin® , magnesium aluminometasilicate, known under trade name Neusilin. The porous carriers exemplified above are free-flowing which is advantageous during the handling and the preparation of the drug delivery system, i.e. the porous particles containing the adsorbed active ingredient. The porous particle, comprising the drug, may be used for direct compression into a multiple unit tableted [illegible], but another example of suitable dosage forms are capsules filled with the porous particles.

The porous particle material used as carrier shall have a particle size of between 50-500 µm, preferably a size between 100 – 150 µm.

The liquid adsorption capacity of the particles is between 0.70 – 4.0 ml/g.

The pore size should be between 10-1000Å, most preferably between 50-500Å.

Features of the invention are compositions comprising NO-donating NSAIDs in oily form such as NO-donating naproxen, NO-donating diclofenac, NO-donating ketoprofen etc (according to Formula Ia, Ig, Ic, If and IL). The invention is not in any way restricted to these compositions.

The active ingredient is characterised by low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption

from the gastro-intestinal tract (GIT) may be dissolution rate limited resulting in poor bioavailibility upon oral administration. By having the NO-donating NSAID finely dispersed, either as the solely component adsorbed into the porous particles or as SEDDs adsorbed into the porous particles, an enhanced absorption can be obtained. Also a controlled absorption of the NO-donating NSAID is obtained.

The releasing rate of the active ingredient from the composition is also depending on the presence or absence of a surfactant. It has been shown that the release characteristics can be changed by adding a surfactant. The rate of release may increased if a suitable surfactant is present, together with the active ingredient, into the porous particle. This property can be utilised in the design of the dosage form. A pharmaceutical dosage form comprising NO-donating NSAID may comprise both porous particles with absorbed pure NO-donating NSAID and porous particles with absorbed NO-donating NSAID in admixture with a surfactant. By mixing these different porous particles, the rate of release profile can easily be modified.

The surfactant is added to the active ingredient before adding the porous particles. The components can also be melted before the mixing to get a homogeneous mixture of the two components before the adding the porous particles. The wording "surfactant" is defined as surface-active amphiphilic compounds such as block co-polymers. Preferred surfactants in accordance with the present invention are non-ionic surfactants, for example those containing polyethylene glycol (PEG) chains, particularly block co-polymers such as poloxamers.

Examples of suitable poloxamers are Poloxamer 407 (Pluronic F127®); Poloxamer 401 (Pluronic L121®); Poloxamer 237 (Pluronic F87®); Poloxamer 338 (Pluronic F138®); Poloxamer 331 (Pluronic L101®); Poloxamer 231 (Pluronic L81®); tetrafunctional polyoxyethylene polyoxypropylene block copolymer of ethylene diamine, known as Poloxamine 908 (Tetronic 908®); Poloxamine 1307 (Tetronic 1307®); Poloxamine 1107; polyoxyethylene polyoxybutylene block copolymer, known as Polyglycol BM45® . This

list is only intended to serve as exemplification of surfactants that may be used in accordance with the present invention, and should not in any way be considered as exhaustive or as limiting the invention.

All surfactants described above are commercially available from e.g. BASF, Dow Chemicals, and Gattefossé. The total amount of surfactant(s) in accordance with the invention may be within the range of from 12.5-6000 mg, preferably of from 100-500 mg. The ratio NO-donating NSAID:surfactant may vary from 1:0.1 to 1:10, preferably from 1:0.3 to 1:3.

In a multiple unit dosage form it is possible to combine porous particles comprising units with adsorbed NO-donating NSAID solely together with porous particles with adsorbed NO-donating NSAID together with a suitable surfactant. This dosage form will administer the NO-donating NSAID with a more complex release profile giving, a first rapid onset by the release from the porous particles comprising the active ingredient combined with the surfactant and, a delayed release from the porous particles comprising the active ingredient solely.

Another combination is a multiple dosage form comprising the high dose NO-donating naproxen with or without surfactant, or combined, in combination with another NO-donating NSAID, for example NO-donating diclofenac, with or without surfactant, or combined.

Preparation of the composition

The incorporation of the NO-donating NSAID, in oily form, into the porous particles may be accomplished by conventional known methods. One method is to mix the oily substance directly with the porous particle material. Alternatively, the oily substance can be dissolved in a suitable solvent, such as an alcohol for example, ethanol. The porous particles are then added and the active substance is adsorbed. The solvent is then evaporated and the particles are collected.

The porous particles comprising adsorbed NO-donating NSAIDs can be prepared in different ways, for example by mixing the oily NO-donating NSAIDs with the porous particles in a mortar, or by dissolving the oily NO-donating NSAIDs in ethanol. The NO-donating NSAID may be mixed with a liquid surfactant, and the resulting mixture is adsorbed to porous particles. The porous particles comprising NO-donating NSAIDs in oily form, are mixed with pharmaceutical acceptable tablet excipients such as fillers, binders, disintegrants and /or pharmaceutically additives, and, optionally, an additional active compound.

Optionally, the prepared porous particles, comprising the NO-donating NSAID, are mixed with a second active ingredient, enteric coating layered pellets comprising a proton pump inhibitor, and compressed into tablets.

When the porous particles, loaded with the oily NO-donating NSAID according to the invention, are used in a drug delivery system, they may be used as such or filled into capsules, compressed into tablets by ways well known in the art. The filling into capsules, compressing to tablets should be performed in a manner that the fast release characteristics are not substantially changed. If fast release in the small intestine is desired, the loaded porous particles could be enteric coated. It has also been shown by the present invention that the release characteristics are changed by adding a suitable surfactant. The porous particles comprising a mixture of the active ingredient and a surfactant, have a more fast release than the particles without the surfactant. By mixing loaded porous particles, i.e. mixing porous particles comprising both a drug and a surfactant with porous particles with only a drug, into one dosage form, for example capsule or tablet, the release characteristics can be modified. According to a release profile when this dosage form is administered, one dose is administered with a quick onset, the remaining dose is administered with a slower release.

Some of the NO-donating NSAIDs are high dose drugs. Therefore, an important part of the invention is the possibility to produce a divisable dosage form, for example, a divisable tablet.

The total amount of NO-donating NSAID(s) used in the composition of the invention is preferably in the range 50-1500 mg per unit dose. In still a further preferred embodiment, the amount of NO-donating NSAID(s) used in the composition is 125-500 mg per unit dose.

The porous particles comprising the active ingredient is mixed with conventional tablet excipients such as binders, fillers etc. Example of suitable excipients is microcrystalline cellulose and polyvinyl pyrrolidon, hydroxypropyl methylcellulose (HPMC), lactose, sodium carboxymethylceullolose (NaCMC).

The prepared tablet may be coated by conventional film coat or sugar coat, to obtain tablets of good appeareance. Suitable layering material for the film coat are derivatives of cellulose, such as hydroxypropylmethylcellulose, methylcellulose or ethylcellulose and acrylate-based polymers. Sugar coating involves successive application of sucrose based-based solutions to the tablets.

unit dose" is defined as the amount of active compound administered in one tablet, in one single capsule or a sachet.

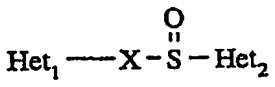
Combinations

It is well known that patient compliance is a main factor in receiving a good result in medical treatments. An improved patient compliance is obtained by administering the different drug in only one dosage form. By the present invention, new oral dosage forms comprising two or more different active substances combined in one fixed unit dosage form, in a multiple unit tableted dosage form are shown. The dosage form will simplify the regimen and improve the patient compliance.

Thus, one embodiment is to mix spherical porous particles with different absorbed NO-donating NSAIDs. For example, by a combination of both the NO-donating diclofenac

and NO-donating NSAID it is possible to obtain a dosage form with a fast immediate release of the NO-donating diclofenac and a good maintenance administering by the NO-donating naproxen.

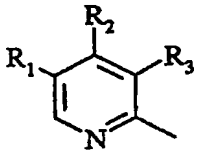
The porous particles containing the absorbed NO-donating NSAID can also be combined with other drugs i.e. as a combination of two or several drugs each having special requirements for being administered. The NO-donating NSAIDs can be combined with drugs such as, for instance, anti-ulcer drugs. The porous particles comprising a NO-donating NSAID according to the present invention can be combined with enteric coated pellets comprising a proton pump inhibitor, such as omeprazole. The H^+, K^+-ATPase inhibitors are one interesting group of substances for combination with the NO-donating NSAID. Examples of specifically interesting compounds of the H^+, K^+-ATPase inhibitors are the acid susceptible proton pump inhibitors, for example compounds of the general formula II below. Even if NO-donating NSAIDs have an improved side-effect profile with respect to NSAIDs, the administration of the NO-donating NSAID together with a proton pump inhibitor might be a successful combination of drugs.



II

wherein

Het_1 is



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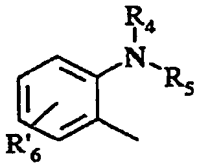
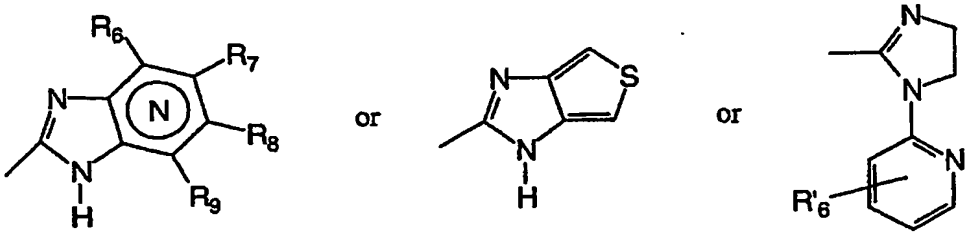
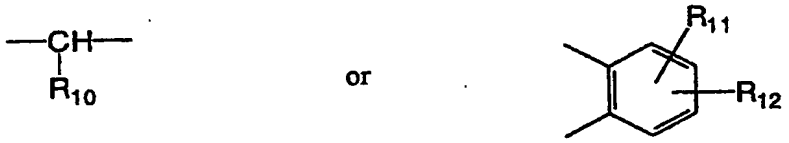


Het_2 is



X =



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any sub

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6 is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl and the alkyl groups.

The alkyl groups, alkoxy groups and moieties thereof, included in the substituents R_1- R_{12} above may be branced or straight C_1-C_9-chains or comprise cyclic alkyl groups, such as cyclo-alkyl-alkyl.

Examples of proton pump inhibitors are omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole. These examples are not in any way a restriction of possibilities.

The acid susceptible proton pump inhibitors used in the dosage forms of the invention may be used in their neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+},Ca^{2+},Na^+ , K^+ or Li^+salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of the substantially pure enantiomer thereof, salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 (magnesium omeprazole) and WO94/27988 (the single enantiomers of omeprazole salts).

The proton pump inhibitors used in a combination in accordance with the present invention, are preferably provided as enteric coating layered pellets comprising the acid susceptible proton pump inhibitor. For the composition of the enteric coating layered pellets and its preparation, reference is made to WO 96/01623, which is hereby incorporated by reference

The enteric coated pellets comprising the proton pump inhibitor is combined with the porous particles comprising the NO-donating NSAID according to the present invention. The pellets and the porous particles are compressed into a tablet.

Suitable combinations in accordance with the present invention are for instance a NO-donating NSAID of the formula Ia (NO-donating naproxen) and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole; or a NO-donating NSAID of the formula Ig (NO-donating diclofenac) and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor (in the form of a racemat, an alkaline salt or one of its single enantiomers) and one or more NO-donating NSAID is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the porous particles prepared according to the present invention comprising the NO-donating NSAID(s) and conventional excipients. The NO-donating NSAID(s) and tablet excipient may also be in the form of granules. The dry mixture of enteric coating layered units comprising the proton pump inhibitor, the NO-donating NSAID porous particles according to the present invention are compressed into multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, porous particles, granules or pellets, in the following referred to as pellets of the acid susceptible proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets comprising the acid susceptible proton pump inhibitor. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layers(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistances does not decrease more than 10 % during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or th 0.1 M HCL (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperaure of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coateing layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

Examples

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention. The examples show the manufacturing of the dosage forms comprising porous particles with NO-donating naproxen, dosage forms comprising porous particles with NO-donating naproxen, mixed with surfactant, together with porous particles with NO-donating diclofenac. Also, an example showing a dosage forms with a combination of NO-donating NSAIDs and the proton pump inhibitor omeprazole is presented.

Experiments with one NO-donating NSAID (NO-donating naproxen)

NO-donating naproxen (Compound of formula Ia) comprising free-flowing powder was made by making a mixture of the below mentioned composition. The components are mixed with a pestle in a mortar:

A) Compound of formula Ia /Neusilin 1/1

12.50 g Compound of formula Ia
12.50 g Neusilin

B) Compound of formula Ia / Neusilin ½

8.33 g Compound of formula Ia
16.67 g Neusilin

C) Compound of formula Ia / Neusilin 2/1

16.67 g Compound of formula Ia
8.33 g Neusilin

D) Compound of formula Ia /Fujicalin 1/1.5

10 g Compound of formula Ia
15 g Fujicalin

E) Compound of formula Ia /Fujicalin 1/1.25

11 g Compound of formula Ia
13.75 g Fujicalin

F) Compound of formula Ia /Ca-silikat ¼

5 g Compound of formula Ia
20 g Ca-silikat

After the above mentioned mixtures were sieved through a 0.5 mm sieve, and mixed with tablet excipients according to mixture 1 and mixture 2, respectively.

Excipient mixture 1

48.30 g Microcrystalline cellulose (Avicel pH 102)

1.65 g Polyvinyl pyrrolidone, cross-linked
0.15 g Sodium stearyl fumarate

Excipient mixture 2

48.30 g Microcrystalline cellulose (Avicel pH 102)
1.65 g Polyvinyl pyrrolidone, cross-linked

The components were mixed according the following and the obtained mixtures were compressed into tablets, weighing 1200 mg, using a tablet machine rigged with 18 mm oval punches into following compositions:

Composition 1:
Tablets, 640 mg Compound of formula Ia

10 g Compound of formula Ia / Neusilin 2/1
2.5 g Excipient mixture 1

Composition 2:
Tablets, 320 mg Compound of formula Ia

10 g Compound of formula Ia / Fujicalin 1/2
2.5 g Excipient mixture 1

Composition 3:
Tablets, 200 mg Compound of formula Ia

6 g Compound of formula Ia / Fujicalin 1/2
6 g Excipient mixture 1

Composition 4:
Tablets, 300 mg Compound of formula Ia

6 g Compound of formula Ia / Neusilin 1/1
6 g Excipient mixture 1

Composition 5:
Tablets, 200 mg Compound of formula Ia

6 g Compound of formula Ia / Neusilin 1/2
6 g Excipient mixture 1

Composition 6:
Tablets, 240mg Compound of formula Ia

6 g Compound of formula Ia / Fujicalin 1/1.5
6 g Excipient mixture 2

Composition 7:
Tablets, 240mg Compound of formula Ia

6 g Compound of formula Ia / Fujicalin 1/1.25
6 g Excipient mixture 2

Composition 8:
Tablets, 375mg Compound of formula Ia

9.38 g Compound of formula Ia / Fujicalin 1/1.5
2.62 g Excipient mixture 2

Composition 9:
Tablets, 375mg Compound of formula Ia

8.44 g Compound of formula Ia / Fujicalin 1/1.25

3.56 g Excipient mixture 2

Composition 10:

Tablets, 120 mg Compound of formula Ia

10 g Compound of formula Ia /Ca-silikat 1/4

10 g Excipient mixture 1

Results

The dissolution rate is determined both by using a thermostated beaker with a stirrer (50 rpm) and USP paddle bath (USP dissolution test No. 2), operated at 50 rpm. The dissolution medium has a temperature of 37°C. The media used was phosphate buffer pH = 6.8, containing 8.8 mg/litre of CTAB (cetyltrimethylammonium bromide). The increase in absorbance corresponded to the release of NO-donating naproxen (according to compound of Formula Ia).

Further there is a demand on the amount and art of dissolution medium, that it enables for the whole dose to be tested a non-retarded homogenous distribution of liberated.

Composition 1. Tablet, 640 mg

Time	% Released
5 min	1
10 min	4.9
15 min	12.1
30 min	24.3
60 min	38.1

Composition 2. Tablet, 320 mg

Time	% Released
5 min	15
10 min	30

15 min	40
30 min	50
60 min	60

Composition 3. Tablet, 200 mg

Time	% Released
5 min	26.5
10 min	51.4
15 min	61.6
30 min	83
60 min	91

Composition 4. Tablet, 300 mg

Time	% Released
5 min	2
10 min	5.5
15 min	8.3
30 min	17.2
60 min	28.5

Composition 5. Tablet, 200 mg,

Time	% Released
5 min	1
10 min	1
15 min	2.3
30 min	5.7
60 min	9.1

Composition 6. Tablet, 240 mg

Time	% Released
5 min	31.5
10 min	51.9
15 min	63.1
30 min	83
60 min	98.2

Composition 7.Tablet, 267 mg

Time	% Released
5 min	26.7
10 min	43.6
15 min	56.5

30 min	78.9
60 min	97.8

Composition 8. Tablet, 375 mg

Time	% Released
5 min	19
10 min	30.5
15 min	37.5
30 min	52
60 min	59

Composition 9. Tablet, 375 mg

Time	% Released
5 min	18.9
10 min	31.5
15 min	40.5
30 min	51.6
60 min	62

Composition 10. Tablet, 120 mg

Time	% Released
10 min	23
20 min	37
30 min	47
40 min	55
60 min	67

Following experiments show compositions comprising the NO-donating NSAID mixed with a surfactant before the absorption into the porous particle.

A mixture of Compound of formula Ia and a surfactant was prepared by melting and mixing the surfactant and the active at 60 °C.

Compound of formula Ia /Pluronic F87 1/0.3

4 g Compound of formula Ia

1.2 g Pluronic F87

A free-flowing powder comprising the Compound of formula Ia was made by adding the above mentioned mixture to porous particles, by mixing the components with a pestle in a mortar, at 60 °C.

Compound of formula Ia /Pluronic F87 1/0.3)/Fujicalin 1/4

2 g Compound of formula Ia / Pluronic F87

8 g Fujicalin

The above mentioned mixtures were sieved through a 0.5 mm sieve and mixed.

Excipient mixture

16.10 g Microcrystalline cellulose (Avicel pH 102)

0.55 g Polyvinyl pyrrolidone, cross-linked

in the following

Composition 11:

Tablets, 92 mg Compound of formula Ia

5 g Compound of formula Ia /Pluronic F87 1/0.3)/Fujicalin 1/4

5 g Excipient mixture

The obtained mixtures were compressed into tablets, weighing 1200 mg, using a tablet machine rigged with 18 mm oval punches.

Results

The dissolution rate was detemined in a thermostated beaker with a stirrer (50 rpm).The media used was phosphate buffer pH = 6.8, containing 8.8 mg/litre of CTAB

(cetyltrimethylammonium bromide). The increase in absorbance corresponded to the release of NO-donating naproxen, Compound of formula Ia

Composition 11. Tablet, 92 mg

Time	% Released
5 min	80
10 min	96
15 min	99
30 min	100
60 min	100

Experiments with two different NO-donating NSAIDs (NO-donating naproxen/ NO-donating diclofenac).

Experiments were performed with compositions comprising NO-donating diclofenac, Compound of Formula Ig, and NO-donating naproxen mixed with surfactant. Free-flowing powder comprising Compound of formula Ig was made by making a mixture of the below mentioned composition, by mixing the components with a pestle in a mortar:

A. Compound of formula Ig / Fujicalin ½

3 g Compound of formula Ig
6g Fujicalin

A mixture of Compound of formula Ia and a surfactant was prepared by melting and mixing the surfactant and the active at 60 °C.

B. Compound of formula Ia 7/Pluronic F87 1/0.3

3.08 g Compound of formula Ia
0.92 g Pluronic F87

NO-naproxen comprising free-flowing powder was made by adding the above mentioned mixture to porous particles, by mixing the components with a pestle in a mortar, at 60 °C.

(Compound of formula Ia /Pluronic F87 1/0.3)/Fujicalin 1/3

3 g Compound of formula Ia/Pluronic F87
9 g Fujicalin

The above mentioned mixtures were sieved through a 0.5 mm sieve and mixed with,

Excipient mixture
16.10 g Microcrystalline cellulose (Avicel pH 102)
0.55 g Polyvinyl pyrrolidone, cross-linked

in the following compositions:

Composition12:

Tablets, 120 mg Compound of formula Ig

3.60 g mixture A
8.40 g Excipient mixture

Compostion 13:

Tablets, 120 mg Compound of formula Ia

6.24 g mixture B
5.76 g Excipient mixture

Composition14:

Tablets, 120 mg Compound of formula Ig and Compound of formula Ia

1.80 g mixture **A**

3.12 g mixture **B**

7.08 g Excipient mixture

The obtained mixtures were compressed into tablets, weighing 1200 mg, using a tablet machine rigged with 18 mm oval punches.

Results

Dissolution tests were made in a thermostated beaker with a stirrer (50 rpm). The media used was phosphate buffer pH = 6.8, containing 8.8 mg/litre of CTAB (cetyltrimethylammonium bromide). The increase in absorbance corresponded to the release of Compound of formula Ig.

Composition 12, Tablet, 120 mg Compound of formula Ig

Time	% Released
5 min	20
10 min	37
15 min	44
30 min	78
60 min	100

Composition 13. Tablet, 120 mg Compound of formula Ia

Time	% Released
5 min	60
10 min	77
15 min	82
30 min	100
60 min	100

Composition 14. Tablet, 120 mg Compound of formula Ig and Compound of formula Ia

Time	% Released
5 min	60
10 min	80
15 min	100
30 min	100
60 min	100

Experiments with a combination of a NO-donating NSAID and a H^+, K^+-ATPase inhibitor.

Experiment with NO-d[illegible]roxen mixed with H^+, K^+-ATPase inhibitors. Following experiment show a [illegible]nprising the compound of formula Ia adsorbed into the spherical porous particle[illegible]ixed with enteric coated pellets comprising acid susceptible proton pump inhibitor.

Composition 15:

Multiple unit tableted dosage form comprising compound of formula Ia 250 mg and omeprazole 20 mg (as Mg-Omeprazole).

Principle; Enteric coated overcoated pellets comprising omeprazole were manufactured separately, as was the NO-donating naproxen comprising powder mixture before compressing the two components together with tabletting excipients into tablets.

Free-flowing powder comprising compound of formula Ia was made by making a mixture of

Compound of formula Ia 250 parts by weight

Calcium silicate 250 parts by weight

in a mortar and working these compounds together. This mixture (500 parts by weight), a free-flowing powder, was sieved through a 0.5 mm sieve.

The enteric coated omeprazole pellet was made by the following:

Core material (omeprazole)		
Magnesium omeprazole	15.00	kg
Non-pareil seeds	15.00	kg
Hydroxypropyl methylcellulose	2.25	kg
Water purified	40	kg
Application of separating layer		
Core material (acc. to above)	15.00	kg
[illegible]oxypropyl cellulose	1.50	kg
[illegible]	2.57	kg
Magnesium Stearate	0.21	kg
Water purified	20	kg
Enteric coating(omeprazole)		
Separating layered pellets (acc. to above)	18.00	kg
Methacrylic acid copolymer (30% suspension)	7.92	kg
Triethyl citrate	2.38	kg
Mono- and diglycerides (NF)	0.40	kg
Polysorbate 80	0.04	kg
Water purified	17	kg
Over-coating(omeprazole)		
Enteric coated pellets	25.00	kg
Hydroxypropyl methylcellulose	0.31	kg

Mg-Stearate	0.009	kg
Water purified	6	kg

The suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert non-pareil seeds from a water suspension containing the dissolved binder (hydroxypropylmethylcellulose).

The prepared core material was provided with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the separating layered pellets in a fluid bed apparatus. In the same type of apparatus the enteric coated pellets were coated with hydroxypropyl methylcellulose/Mg-Stearate suspension. The over-coated pellets were sieved to remove possible agglomerates. Average medium particle size of the obtained pellets was around 0.5 mm in diameter.

The free-flowing powder comprising the NO-donating NSAID was (500 parts by mixed with:

Enteric coated overcoated omeprazole pellets (from above)	100	parts by weight
Microcrystalline cellulose (Avicel pH 102 special coarse grade)	482	parts by weight
Polyvinyl pyrrolidone, cross-linked	16.5	parts by weight
Sodium stearylfumarate	1.5	parts by weight

Enteric coated overcoated omeprazole component pellets were manufactured by charging components in proportions according to the recipe below;

The obtained mixture of porous particles comprising the compound of formula Ia and the enteric coated pellets comprising omeprazole was compressed in a tabletting machine to tablets having an average weight of 1095 mg, using 20 mm in diameter flat punches. Tablet hardness was 5-6 kP.

Results

Omeprazole release was tested in USP dissolution apparatus No. 2 (paddle), operated at 100 rpm. After preexposure to simulated gastric juice for 2 hours the release was measured in 900 ml of phosphate buffer having a pH of 6.8, and after 30 minutes 90 % of stated amount had been released.

For the release of the NO-donating naproxen (compound of formula Ia) the same kind of apparatus was used and operated at 100 rpm. As dissolution media 1000 ml of phospahte buffer having a pH of 6.8 and also containing 8.8 mg/ml of CTAB (cetyltrimethylammonium bromide).
The release was followed spectrophotometrically at 269 nm. The absorbance increase corresponded to the following release of NO-donating naproxen (Compound of formula Ia);

Composition 15, Tablet

Time	% Released
30 min	36
60 min	77
90 min	86
120 min	92
180 min	99

Claims:

1. A solid drug delivery composition characterised in that an oily NO-donating Non Steroidal Antiinflammatory Drug (NO-donating NSAID) in oily form is absorbed into a carrier in form of porous particles.

2. A solid drug delivery composition according to claim 1 wherein the porous particles consists of calcium silicate, dibasic calcium phosphate anhydrous, magnesium aluminometasilicate or pregelatinised starch.

3. A solid drug delivery composition according to claims 1 and 2 wherein the porous particles are spherical with a particle size of 50 to 500 µm.

4. A solid drug delivery composition according to claim 3 wherein the particle size of the spherical porous particles is 100 to 150 µm.

5. A solid drug delivery composition according to any of claims 1 to 4 wherein the NO-donating NSAID is NO-donating naproxen.

6. A solid drug delivery composition according to any of claims 1 to 5 wherein the NO-donating NSAID is 4-(nitrooxy)butyl-(S)-2-(9-methoxy-2-naphtyl)-propanoate.

7. A solid drug delivery composition according to any of claims 1 to 4 wherein the NO-donating NSAID is NO-donating diclofenac.

8. A solid drug delivery composition according to claim 7 wherein the NO-donating NSAID is 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 4-(nitrooxy)-butyl ester.

9. A solid drug delivery composition according to any of claims 1 to 8 wherein the particles comprising the NO-donating NSAID are compressed together with tablet excipients into a tablet.

10. A solid drug delivery composition according to claim 9 wherein the tablet is coated.

11. A solid drug delivery composition according to claims 1 to 8 wherein the particles comprising the NO-donating NSAID are encapsulated in a capsule.

12. A solid drug delivery compisition according to claims 1 to 12 wherein the NO-donating NSAID is adsorbed together with a surfactant into the porous particle.

13. A solid drug delivery composition according to claim 12 wherein the surfactant is non-ionic.

14. A solid drug delivery composition according to claim 12 wherein the surfactant is a block co-polymer.

A solid drug delivery composition according to any of claims 12 to 14 wherein the ...nt is a poloxamer.

16. A solid drug delivery composition according to any of claims 12 to 14 wherein the surfactant is a polyoxyethylene polyoxybutylene block copolymer.

17. A solid drug delivery composition according to 1 to 16 wherein the ratio NO-donating NSAID : surfactant is within the range of from 1:0.1 – 1:10.

18. A solid drug delivery composition according to 1 to 16 wherein the ratio NO-donating NSAID : surfactant is within the range of from 1:0.3 – 1:3.

19. A solid drug delivery composition according to claims 1 to 18 comprising a specified amount porous particles with absorbed pure active ingredient and a specified amount porous particles with adsorbed active ingredient mixed with an surfactant altogether mixed with a suitable excipient and compressed into a tablet.

20. A solid drug delivery composition according to claims 9 to 19 wherein the porous particles comprising the NO-donating NSAID, optionally mixed with a surfactant, are mixed together with enteric coated pellets comprising H^+, K^+-ATPase inhibitor.

21. A solid drug delivery composition according to any of claim 9 to 20 wherein the porous particles comprising NO-donating naproxen, NO-donating diclofenac, NO-donating ketoprofen or NO-donating ketorolac, optionally mixed with a surfactant, are mixed together with enteric coated pellets comprising omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole or a pharmaceutical acceptable salt thereof.

22. Process for producing the porous particles comprising the NO-donating NSAID in oily form according to claims 1 to 8 characterised in mixing the NO-donating NSAID, optionally melted, with porous particles.

23. Process for producing the porous particles comprising the absorbed NO-donating NSAID according to claims 1 to 8 characterised in:

a) dissolving the NO-donating NSAID in an alcohol,
b) adding the porous particles during stirring,
c) evaporating the added alcohol,
d) recovering the porous particles comprising the absorbed NO-donating NSAID.

24. Process for producing porous particles comprising the NO-donating NSAID and an surfactant according to claims 12 to 16 characterised in:

a) mixing the NO-donating NSAID with an surfactant,
b) adding the porous particles,
c) stirring,
d) recovering the porous particles containing the absorbed NO-donating NSAID and the surfactant.

25. Process for producing the porous particles comprising the NO-donating NSAID and a surfactant characterised in:

a) melting of the NO-donating NSAID together with the surfactant,

b) adding the porous particles,

c) stirring,

d) recovering the porous particles containing the absorbed NO-donating NSAID and the surfactant.

26. Use of a dosage form according to any of the claims 1 to 21 for the manufacture of medicament for treating pain.

27. Use of a dosage form according to any of the claims 1 to 21 for the manufacture of medicament for treating inflammation.

28. A method for the treatment of pain comprising oral administering to a patient suffering therefrom a solid dosage form comprising a NO-donating NSAID according to claims 1 to 21.

29. A method for the treatment of inflammation comprising oral administering to a patient suffering therefrom a solid dosage form comprising a NO-donating NSAID according to claims 1 to 21.

Abstract

The present invention claims and discloses a solid drug delivery composition for administering NO-donating NSAIDs in oily form orally. The solid drug delivery composition comprises a carrier in form of porous particles and with the NO-donating NSAID adsorbed in it. The NO-donating NSAID may also be combined with a surfactant. Also a solid drug delivery composition comprising a combination of active ingredients are disclosed by the invention, for instance, combination of porous particles comprising different NO-donating NSAIDs, combination of porous particles comprising NO-donating NSAID with enteric coated pellets comprising H^+, K^+-ATPase inhibitor. Also a process for producing the solid drug delivery composition, the use of it in the method for treating pain and inflammation is disclosed by the invention.